

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
LUBISCH et al. ) Applications

Serial No. Not Assigned )

Filed: )

For: DIBENZODIAZEPINE DERIVATIVES, THEIR PREPARATION AND USE

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as shown in the attached sheets.

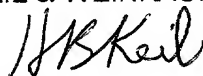
REMARKS

The claims have been amended to eliminate multiple dependency. No new matter has been added. A clean copy of the claims is attached.

Entry of the above amendment is respectfully solicited.

Respectfully submitted,

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2004156-011000

CLEAN VERSION OF AMENDED CLAIMS - 33827-US-009

2. Compounds of the formula I according to claim 1, in which
- A denotes a benzo ring,
  - X<sup>1</sup> denotes O, and
  - R<sup>1</sup> denotes hydrogen.
3. Compounds of the formula I according to claim 1, in which
- B denotes phenyl, cyclohexyl, piperidine, pyridine, pyrimidine, pyrrole, pyrazole, thiophene, furan, oxazole, naphthalene, piperazine, quinoline, pyrazine or indole, each of which can be substituted by one R<sup>4</sup> or at most 2 R<sup>5</sup>.
4. Compounds of the formula I according to claim 1, in which
- L denotes a carbon chain which has from 1 to 8 C atoms and which contains at least one triple bond, where the carbon atoms of the chain can be substituted by one or two R<sup>4</sup> radicals and at most two different or identical R<sup>5</sup> radicals,
  - v denotes 1, and
  - w denotes 0 or 1.
5. Compounds of the formula I according to claim 1, in which
- R<sup>4</sup> denotes D<sub>0,1</sub>-F<sup>1</sup><sub>0,1</sub>-G<sup>2</sup>-G<sup>3</sup>, where G<sup>3</sup> denotes hydrogen,
  - D denotes O or NR<sup>43</sup>, where R<sup>43</sup> denotes hydrogen or C<sub>1</sub>-C<sub>3</sub>-alkyl, and
  - F<sup>1</sup> denotes C<sub>2</sub>-C<sub>4</sub>-alkyl.
6. Compounds of the formula I according to claim 1, in which

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R<sup>4</sup> denotes G<sup>1</sup>-F<sup>1</sup><sub>0</sub>, -G<sup>2</sup>-G<sup>3</sup>, where G<sup>3</sup> denotes hydrogen, and

F<sup>1</sup> denotes C<sub>1</sub>-C<sub>2</sub>-alkyl.

7. Compounds of the formula I according to claim 6, in which

G<sup>1</sup> denotes imidazole or pyrrole, where the pyrrole can in each case be substituted by at most three different or identical R<sup>5</sup> radicals, and

F<sup>1</sup> denotes C<sub>1</sub>-C<sub>2</sub>-alkyl.

8. Pharmaceutical composition which comprises at least one compound according to claim 1 and also at least one customary carrier and/or auxiliary substance.

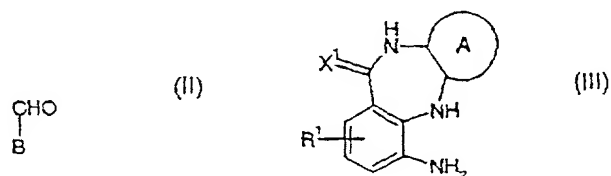
9. Use of a compound of formula I according to claim 1 for producing a pharmaceutical for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial infarction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections.

10. Process for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial

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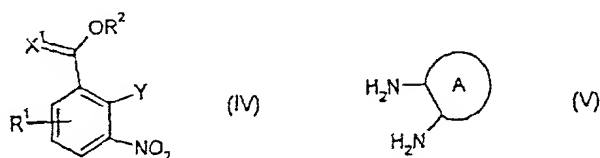
infraction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections by administration of an effective quantity of at least one compound of the formula I according to claim 1.

11. Process for producing a compound according to claim 1, which comprises condensing an aldehyde of the formula II with a diamine of the formula III:



where the symbols in the formulae II and III have the same meaning as in claim 1.

12. Process according to claim 11, where the diamine of the formula III is obtained by reacting a substituted nitrobenzoic ester of the formula IV with a diamine of the formula V, in a polar solvent and in the presence of a base, and subsequently hydrogenating:



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where the symbols in the formulae IV and V have the same meaning as in Claim 1 and R<sup>2</sup> denotes branched or unbranched, saturated or unsaturated C<sub>1</sub>-C<sub>6</sub>-alkyl.

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MARKED VERSION OF AMENDED CLAIMS - 33827-US-009

2. Compounds of the formula I according to [Claim] claim 1, in which
- A denotes a benzo ring,
  - X<sup>1</sup> denotes O, and
  - R<sup>1</sup> denotes hydrogen.
3. Compounds of the formula I according to claim 1 [Claim 1 or 2], in which
- B denotes phenyl, cyclohexyl, piperidine, pyridine, pyrimidine, pyrrole, pyrazole, thiophene, furan, oxazole, naphthalene, piperazine, quinoline, pyrazine or indole, each of which can be substituted by one R<sup>4</sup> or at most 2 R<sup>5</sup>.
4. Compounds of the formula I according to claim 1 [at least one of Claims 1 to 3], in which
- L denotes a carbon chain which has from 1 to 8 C atoms and which contains at least one triple bond, where the carbon atoms of the chain can be substituted by one or two R<sup>4</sup> radicals and at most two different or identical R<sup>5</sup> radicals,
  - v denotes 1, and
  - w denotes 0 or 1.
5. Compounds of the formula I according to claim 1 [at least one of Claims 1 to 4], in which
- R<sup>4</sup> denotes D<sub>0,1</sub>-F<sup>1</sup><sub>0,1</sub>-G<sup>2</sup>-G<sup>3</sup>, where G<sup>3</sup> denotes hydrogen,
  - D denotes O or NR<sup>43</sup>, where R<sup>43</sup> denotes hydrogen or C<sub>1</sub>-C<sub>3</sub>-alkyl, and

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F<sup>1</sup> denotes C<sub>2</sub>-C<sub>4</sub>-alkyl.

6. Compounds of the formula I according to claim 1 [at least one of Claims 1 to 4],  
in which

R<sup>4</sup> denotes G<sup>1</sup>-F<sup>1</sup><sub>0</sub>, -G<sup>2</sup>-G<sup>3</sup>, where G<sup>3</sup> denotes hydrogen, and

F<sup>1</sup> denotes C<sub>1</sub>-C<sub>2</sub>-alkyl.

7. Compounds of the formula I according to [Claim] claim 6, in which

G<sup>1</sup> denotes imidazole or pyrrole, where the pyrrole can in each case be  
substituted by at most three different or identical R<sup>5</sup> radicals, and

F<sup>1</sup> denotes C<sub>1</sub>-C<sub>2</sub>-alkyl.

8. Pharmaceutical composition which comprises at least one compound according  
to claim 1 [one of Claims 1 to 7] and also at least one customary carrier and/or  
auxiliary substance.

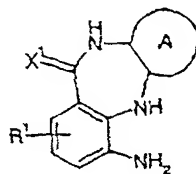
9. Use of a compound of formula I according to claim 1 [one of Claims 1 to 7] for  
producing a pharmaceutical for the prophylaxis and/or treatment of  
neurodegenerative diseases, neuronal damage or damage due to ischaemias,  
for treating microinfarctions, for treating in association with a revascularization of  
critically stenosed coronary arteries or critically stenosed peripheral arteries, for  
treating acute myocardial infarction and damage during and after its medicinal or  
mechanical lysis, for treating tumours and their metastases, and for treating  
sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral  
infections.

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10. Process for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial infraction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections by administration of an effective quantity of at leasts one compound of the formula I according to claim 1 [one of Claims 1 to 7].
11. Process for producing a compound according to claim 1 [one of Claims 1 to 7], which comprises condensing an aldehyde of the formula II with a diamine of the formula III:



(II)



(III)

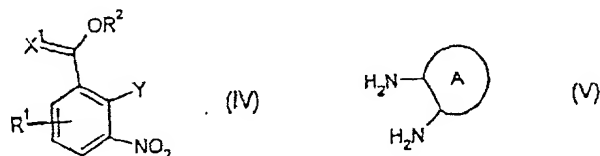
where the symbols in the formulae II and III have the same meaning as in claim [Claim] 1.

12. Process according to claim [Claim] 11, where the diamine of the formula III is



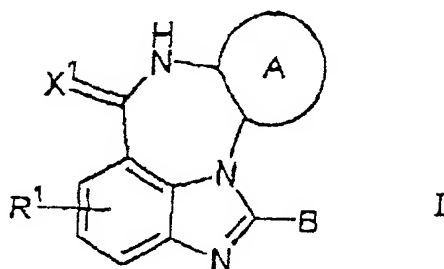
MARKED VERSION OF AMENDED CLAIMS - 33827-US-009

obtained by reacting a substituted nitrobenzoic ester of the formula IV with a diamine of the formula V, in a polar solvent and in the presence of a base, and subsequently hydrogenating:



where the symbols in the formulae IV and V have the same meaning as in Claim 1 and R<sup>2</sup> denotes branched or unbranched, saturated or unsaturated C<sub>1</sub>-C<sub>6</sub>-alkyl.

1. Compounds of the formula I



in which

- A denotes a saturated, unsaturated or partially unsaturated ring having at most 6 carbon atoms or an unsaturated or partially unsaturated ring having at most 5 carbon atoms and from 1 to 3 nitrogen atoms, one oxygen atom and/or one sulphur atom,
- X<sup>1</sup> denotes S, O and NH, and
- R<sup>1</sup> denotes hydrogen, chlorine, fluorine, bromine, iodine, branched and unbranched C<sub>1</sub>-C<sub>6</sub>-alkyl, OH, nitro, CF<sub>3</sub>, CN, NR<sup>11</sup> R<sup>12</sup>, NH-CO-R<sup>13</sup>, or O-C<sub>1</sub>-C<sub>4</sub>-alkyl, where R<sup>11</sup> and R<sup>12</sup>, independently of each other, denote hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkyl, and R<sup>13</sup> denotes hydrogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkylphenyl or phenyl,
- B denotes an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms or an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms, where the respective ring can be additionally substituted by one R<sup>4</sup> and at most 3 different or identical R<sup>5</sup> radicals, and one or two carbon, or sulphur,

atoms can also carry one or two =O groups, such as keto groups, sulphones or sulphoxides, or denotes a radical  $L_v-Y-M_w$ , in which

L denotes a straight-chain or branched saturated or unsaturated carbon chain of from 1 to 8 C atoms, where each carbon atom can be substituted by one or two  $R^4$  radicals and at most two different or identical  $R^5$  radicals,

M possesses, independently of L, the same meaning as L, and

Y denotes a bond, S, O or  $NR^3$ , where  $R^3$  is hydrogen, branched or unbranched  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_4$ -alkylphenyl or phenyl, and

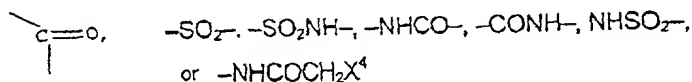
v denotes 0 and 1, and

w denotes 0 and 1,

$R^4$  denotes hydrogen or  $-(D)_p-(E)_s-(F^1)_q-G^1-(F^2)_r-G^2-G^3$ , where

D denotes S,  $NR^{43}$  or O,

E denotes phenyl,



$X^4$  denotes S, O or NH,

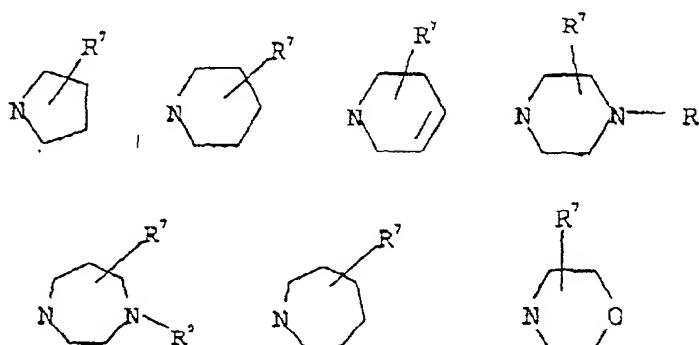
$F^1$  denotes a straight-chain or branched, saturated or unsaturated carbon chain of from 1 to 8 C atoms,

$F^2$  independently of  $F_1$  possesses the same meaning as  $F_1$ ,

$G^1$  denotes a bond, an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms or an unsaturated, saturated or

partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms, where the respective ring can be additionally substituted by at most 3 different or identical R<sup>5</sup> radicals, and one or two carbon and/or sulphur atoms can also carry one or two =O groups, and

G<sup>2</sup> denotes NR<sup>41</sup>R<sup>42</sup>,



or a bond,

G<sup>3</sup> denotes an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms or an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms where the respective ring additionally substituted by at most 3 different or identical R<sup>5</sup> radicals, and one or two carbon, or sulphur, atoms can also carry one or two =O groups, or denotes hydrogen,

p denotes 0 or 1,

s denotes 0 or 1,

- q denotes 0 or 1,
- r denotes 0 or 1,
- $R^{41}$  denotes hydrogen,  $C_1$ - $C_6$ -alkyl, where each carbon atom can additionally carry up to 2  $R^6$  radicals, phenyl, which can additionally carry at most 2  $R^6$  radicals, and  $(CH_2)_t$ -K, and
- $R^{42}$  denotes hydrogen,  $C_1$ - $C_6$ -alkyl,  $-CO-R^8$ ,  $SO_2NH_2$ ,  $SO_2-R^8$ ,  $-(C=NH) -R^8$  and  $(C=NH) -NHR^8$ ,
- $R^{43}$  denotes hydrogen and  $C_1$ - $C_4$ -alkyl,
- t denotes 1, 2, 3 or 4,
- K denotes  $NR^{11}R^{12}$ ,  $NR^{11}$ - $C_1$ - $C_4$ -alkylphenyl, pyrrolidine, piperidine, 1,2,5,6-tetrahydropyridine, morpholine, homopiperidine, piperazine, which can be additionally substituted by an alkyl radical  $C_1$ - $C_6$ -alkyl, and homopiperazine, which can be additionally substituted by an alkyl radical  $C_1$ - $C_6$ -alkyl,
- $R^5$  denotes hydrogen, chlorine, fluorine, bromine, iodine, OH, nitro,  $CF_3$ , CN,  $NR^{11}R^{12}$ ,  $NH-CO-R^{13}$ ,  $C_1$ - $C_4$ -alkyl  $-CO-H-R^{13}$ ,  $COR^8$ ,  $C_0$ - $C_4$ -alkyl-O-CO- $R^{13}$ ,  $C_1$ - $C_4$ -alkylphenyl, phenyl,  $CO_2$ - $C_1$ - $C_4$ -alkyl and branched and unbranched  $C_1$ - $C_6$ -alkyl, O- $C_1$ - $C_4$ -alkyl or S- $C_1$ - $C_4$ -alkyl where each C atom of the alkyl chains can carry up to two  $R^6$  chains can be unsaturated, radicals and the alkyl chains can be unsaturated
- $R^6$  denotes hydrogen, chlorine, fluorine, bromine, iodine, branched or unbranched  $C_1$ - $C_6$ -alkyl, OH, nitro,  $CF_3$ , CN,  $NR^{11}R^{12}$ ,  $NH-CO-R^{13}$  or O- $C_1$ - $C_4$ -alkyl,
- $R^7$  denotes hydrogen,  $C_1$ - $C_6$ -alkyl, phenyl, where the phenyl ring can be additionally

substituted by up to two  $R^{71}$  radicals, and an amine  $NR^{11}R^{12}$  or a cyclic saturated amine having from 3 to 7 members which can additionally be substituted by an alkyl radical  $C_1$ - $C_6$ -alkyl, and homopiperazine which can be additionally substituted by an alkyl radical  $C_1$ - $C_6$ -alkyl,

where the radicals  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  in K,  $R^5$ ,  $R^6$ , and  $R^7$  can, independently of each other, assume meaning as  $R^1$ ,

$R^{71}$  denotes OH,  $C_1$ - $C_6$ -alkyl, O- $C_1$ - $C_4$ -alkyl, chlorine bromine, iodine, fluorine,  $CF_3$ , nitro or  $NH_2$ ,

$R^8$  denotes  $C_1$ - $C_6$ -alkyl,  $CF_3$ , phenyl or  $C_1$ - $C_4$ -alkylphenyl, where the ring can additionally be substituted by up to two  $R^{81}$  radicals,

$R^{81}$  denotes OH,  $C_1$ - $C_6$ -alkyl, O- $C_1$ - $C_4$ -alkyl, chlorine, bromine, iodine, fluorine,  $CF_3$ , nitro or  $NH_2$ , and

$R^9$  denotes hydrogen,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_4$ -alkylphenyl,  $CO_2$ - $C_1$ - $C_4$ -alkylphenyl,  $CO_2$ - $C_1$ - $C_4$ -alkyl,  $SO_2$ -phenyl,  $COR^8$  or phenyl, where the phenyl rings can be additionally substituted by up to two  $R^{91}$  radicals,

$R^{91}$  denotes OH,  $C_1$ - $C_6$ -alkyl, O- $C_1$ - $C_4$ -alkyl, chlorine, bromine, iodine, fluorine,  $CF_3$ , nitro or  $NH_2$ ,

and also their tautomeric forms and possible enantiomeric and diastereomeric forms and their prodrugs.

2. Compounds of the formula I according to claim 1, in which

A denoted a benzo ring,

$X^1$  denotes O, and

- R<sup>1</sup> denotes hydrogen.
3. Compounds of the formula I according to claim 1, in which
 

B denotes phenyl, cyclohexyl, piperidine, pyridine, pyrimidine, pyrrole, pyrazole, thiphen, furan, oxazole, naphthalene, piperazine, quinoline, pyrazine or indole, each of which can be substituted by one R<sup>4</sup> or at most 2 R<sup>5</sup>.
  4. Compounds of the formula I according to claim 1, in which
 

L denotes a carbon chain which has from 1 to 8 C atoms and which contains at least one triple bond, where the carbon atoms of the chain can be substituted by one or two R<sup>4</sup> radicals and at most two different or identical R<sup>5</sup> radicals,

v denotes 1, and

w denotes 0 or 1.
  5. Compounds of the formula I according to claim 1, in which
 

R<sup>4</sup> denotes D<sub>0,1</sub>-F<sup>1</sup><sub>0,1</sub>-G<sup>2</sup>-G<sup>3</sup>, where G<sup>3</sup> denotes hydrogen,

D denotes O or NR<sup>43</sup>, where R<sup>43</sup> denotes hydrogen or C<sub>1</sub>-C<sub>3</sub>-alkyl, and

F<sup>1</sup> denotes C<sub>2</sub>-C<sub>4</sub>-alkyl.
  6. Compounds of the formula I according to claim 1, in which
 

R<sup>4</sup> denotes G<sup>1</sup>-F<sup>1</sup><sub>0</sub>,-G<sup>2</sup>-G<sup>3</sup>, where G<sup>3</sup> denotes hydrogen, and

F<sup>1</sup> denotes C<sub>1</sub>-C<sub>2</sub>-alkyl.
  7. Compounds of the formula I according to claim 6, in which
 

G<sup>1</sup> denotes imidazole or pyrrole, where the pyrrole can in each case be

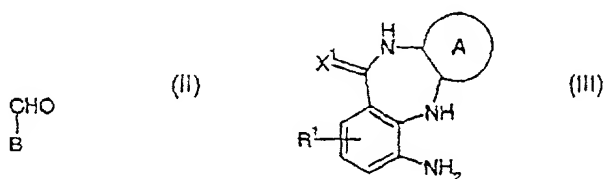
substituted by at most three different or identical  $R^5$  radicals, and

$F^1$  denotes  $C_1$ - $C_2$ -alkyl.

8. Pharmaceutical composition which comprises at least one compound according to claim 1 and also at least one customary carrier and/or auxiliary substance.
9. Use of a compound of formula I according to claim 1 for producing a pharmaceutical for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial infarction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections.
10. Process for the prophylaxis and/or treatment of neurodegenerative diseases, neuronal damage or damage due to ischaemias, for treating microinfarctions, for treating in association with a revascularization of critically stenosed coronary arteries or critically stenosed peripheral arteries, for treating acute myocardial infarction and damage during and after its medicinal or mechanical lysis, for treating tumours and their metastases, and for treating sepsis, multiorgan failure, immunological diseases, diabetes mellitus and viral infections by administration of an effective quantity of at least one compound of the formula I according to claim 1.

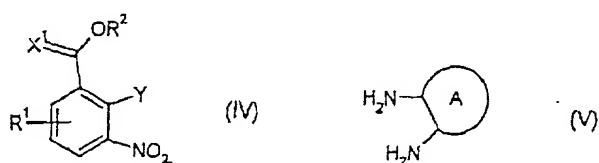


11. Process for producing a compound according to claim 1, which comprises condensing an aldehyde of the formula II with a diamine of the formula III:



where the symbols in the formulae II and III have the same meaning as in claim 1.

12. Process according to claim 11, where the diamine of the formula III is obtained by reacting a substituted nitrobenzoic ester of the formula IV with a diamine of the formula V, in a polar solvent and in the presence of a base, and subsequently hydrogenating:



where the symbols in the formulae IV and V have the same meaning as in Claim 1 and  $\text{R}^2$  denotes branched or unbranched, saturated or unsaturated  $\text{C}_1$ - $\text{C}_6$ -alkyl.